March 22th, 2024

Combined hormonal contraceptive (CHC) – chiormadinone acetate/ethinylestradiol
Slightly increased risk of venous thromboembolism in women using chlormadinone acetate and ethinylestradiol containing combined hormonal contraceptives

Dear Healthcare Professional,

The marketing authorisation holders in agreement with the European Medicines Agency and the AIFA would like to inform you of the following:

Summary

- **The Retrospective Cohort Study RIVET-RCS concluded that women taking combined hormonal contraceptives containing chlormadinone/ethinylestradiol may have a 1.25-fold increased risk of venous thromboembolism (VTE) compared to those taking levonorgestrel. Based on these results, the annual risk of VTE in women taking chlormadinone acetate with ethinylestradiol is estimated at 6-9 VTE cases per 10,000 women.**
- **This compares to an annual incidence of 5-7 VTE cases in 10,000 women who are using low risk combined hormonal contraceptives that contain levonorgestrel, norethisterone, or norgestimate, and to 2 VTE cases per 10,000 women who are not using a combined hormonal contraceptive.**
- **In most women, the benefits of using a combined hormonal contraceptive will outweigh the risk of serious side effects. However, the decision to prescribe a combined hormonal contraceptive should take into consideration the individual woman's current risk factors, particularly those for VTE, and how the risk of VTE compares with other combined hormonal contraceptives. The risk is highest during the first year of using any combined hormonal contraceptive or upon re-starting combined hormonal contraceptives after a break of 4 or more weeks.**
- **Prescribers should raise awareness of the signs and symptoms of VTE and arterial thromboembolism (ATE), which should be described to women when a combined hormonal contraceptive is prescribed and should regularly reassess individual risk factors. Prescribers are reminded that a significant proportion of thromboembolisms are not preceded by any obvious signs or symptoms.**

Background on the safety concern

Combined hormonal contraceptives containing chlormadinone/ethinylestradiol are authorised for hormonal contraception.

The RIVET-RCS pooled analysis is based on four prospective, non-interventional cohort studies comprising 257 481 users of COCs containing CMA or LNG, including 12 710 women exposed to CMA 2 mg/EE 30 µg and 18 669 women exposed to LNG 0.15 mg/EE 30 µg, who were followed up for a total of 25 457 women-years and 33 710 women-years, respectively.

As all included studies did not interfere with prescription behaviour of treating healthcare practitioners and reflected routine contraceptive use in over 200 000 women of reproductive age in a wide geographical range covering 12 European countries and the USA/Canada, the generalisability of these results is deemed high. These data provide a comprehensive insight into the risk profile of components of CMA 2 mg and LNG 0.15 mg, both combined hormonal treatments with EE 30 µg and permits an estimation of risk of VTE in these users.

The study yielded an adjusted Hazard Ratio of 1.25 (95% CI 0.72 – 2.14) for VTE risk with chlormadinone plus ethinylestradiol as compared to levonorgestrel plus ethinylestradiol. However, due to the confidence interval, a two-fold increased risk could not be excluded. Based on these results, the annual risk of VTE in women taking chlormadinone plus ethinylestradiol is estimated at

6-9 VTE cases per 10,000 women. The annual risk of VTE in healthy women using a combined hormonal contraceptive that contains ethinylestradiol plus levonorgestrel, norgestimate or norethisterone is estimated at 5-7 VTE cases per 10,000 women per year. The annual risk of VTE in healthy women not using a combined hormonal contraceptive is estimated at 2 VTE cases per 10,000 women per year (see table 1 below).

Many studies have evaluated the risk of VTE (deep vein thrombosis, pulmonary embolism) among users of different combined hormonal contraceptives. Based on the totality of the data it is concluded that VTE risk slightly differs between products - with the lower risk products being those containing the progestogens levonorgestrel, norethisterone and norgestimate.

Best estimates of the risk of VTE with a number of ethinylestradiol/progestogen combinations compared with the risk associated with levonorgestrel-containing pills are shown in table 1.
Compared with pregnancy and the postpartum period, the risk of VTE associated with using any combined hormonal contraceptives is lower.

Table 1 Risk of VTE with combined hormonal contraceptives (new information in bold)

Progestogen in CHC (combined with ethinylestradiol, unless stated)	**Relative risk vs Levonorgestrel**	**Estimated incidence (per 10,000 women per year of use)**
Non-pregnant non-user	-	2
Levonorgestrel	Ref	5-7
Norgestimate / Norethisterone	1.0	5-7
Nomegestrol (plus Estradiol)	It may present a risk of VTE in the same range as that seen in a levonorgestrel-containing combined hormonal contraceptive.	
Dienogest (plus Estradiol valerate)	It may present a risk of VTE in the same range as that seen in a levonorgestrel-containing combined hormonal contraceptive.	
Chlormadinone acetate	**1.25**	**6-9**
Dienogest	1.6	8-11
Gestodene / Desogestrel / Drospirenone	1.5-2.0	9-12
Etonorgestrel / Norelgestromin	1.0-2.0	6-12

Prescribers should be aware of current product information and clinical guidance when discussing the most suitable type of contraceptive for any woman. The use of any combined hormonal contraceptive increases the risk of VTE compared with no use. The risk is highest during the first year of using any combined hormonal contraceptive or upon re-starting combined hormonal contraceptives after a break of 4 or more weeks. The risk of VTE is also higher in the presence of intrinsic risk factors. Risk factors for VTE change over time and an individual's risk should be re-evaluated periodically. To facilitate earlier diagnosis, all women with signs and symptoms of VTE should be asked if they are taking any medicines "or if they are using a combined hormonal contraceptive".
Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Combined hormonal contraceptives -chlormadinone acetate/ethinyl estradiol may have up to 1.25-fold this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the

woman to ensure she understands the risk of VTE when using combined hormonal contraceptives containing chlormadinone acetate/ethinyl estradiol, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use.

Product information will be updated to reflect our current understanding of the available evidence and to make information as clear as possible.

Attachments to the DHPC:

- checklist that prescribers can consult with the woman in order to prescribe the appropriate Combined hormonal contraceptives;
- patient information sheet which shows the most important signs and symptoms of VTE and ATE so that women are aware of them

Further information for women has been drawn up and is provided on the following website www.agenziafarmaco.gov.it

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with use of chlormadinone acetate/ethinyl estradiol-based medicines via the national spontaneous reporting system to AIFA to https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

AIFA takes this opportunity to remind all healthcare workers of the importance of reporting suspected adverse drug reactions, as an indispensable tool for confirming a favourable benefit/risk ratio in real conditions of use. Reports of Suspected Adverse Drug Reactions must be sent to the Pharmacovigilance Manager of the Structure to which the Operator belongs. This Information Note is also published on the AIFA website (https://www.aifa.gov.it) whose regular consultation is recommended for the best professional information and citizen service.